Author’s response to reviews

Title: Maternal Sport Fish Consumption and Infant Birth Size and Gestation: New York State Angler Cohort Study

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PDF covering letter
Phillippe Grandjean &
David Ozonoff
Editors, Environmental Health

Dear Editors Grandjean and Ozonoff:

We are pleased that our paper entitled “Maternal Sport Fish Consumption and Infant Birth Size and Gestation: New York State Angler Cohort Study” has been invited to be reconsidered following revisions for possible publication in *Environmental Health*. The paper has been extensively revised to reflect the comments from four reviewers. As requested, attached is a point-by-point response to the reviewers’ comments.

We believe the paper has been formatted per the specification of *Environmental Health*. The references are consistent with PubMed and permit automatic linkages.

Please do not hesitate to contact if you should need anything further. We are pleased to have this paper under consideration by *Environmental Health*.

Sincerely yours,

Germaine M. Buck, PhD
Chief, Epidemiology Branch
Reviewer #1 – Goldman

1. Thank you.
2. While our study is unable to analyze PCB concentrations, per se, we do have sufficient power to assess the relation between PCB contaminated sport fish consumption and birth size. Given the characteristics of our study population (i.e., licensed anglers), we do have a lower percentage of low birth weight infants. Although we do have sufficient statistical power for assessing this outcome, we chose to consider all aspects of birth size (including birth weight) in their continuous scale to permit a better understanding of the magnitude of effect of fish consumption and other determinants of fetal growth on infant birth size.
3. We agree that future studies are needed to delineate the beneficial vs. harmful aspects of fish consumption. The absence of a beneficial effect of fish consumption in this study may denote relatively low levels of fish consumption. This is not surprising given that there are long standing advisories in New York State warning women of reproductive age not to eat sport fish.

Reviewer #2 – Hagmar

Major Comments

1. We agree that non-differential misclassification on exposure is a potential limitation of the study as addressed in the discussion. Given the absence of serum for quantification of PCBs in this study, our exposure is sport fish consumption that has been shown to contain PCBs, OCs and other compounds. To this end, our exposure is not PCBs but fish consumption from Lake Ontario (the worst polluted Great Lake) and its tributaries. We only have duration of fish consumption. Frequency of fish consumption was ascertained only in 1991 when the angler families were enrolled into the New York State Angler Cohort Study. This measure was intended to capture recent consumption given New York State’s health advisories warning people not to eat these species of fish. We have noted this on pages 12-14.
2. We only have frequency (# monthly fish meals) for 1991. Hence, this measure of fish consumption pertains to eating after the births of most infants in our study (born between 1986-1991). We did look at the cross-tabulation between duration and 1991 frequency of eating and find the regular eaters tend to still be eating in 1991 while never eaters do not “acquire” eating behaviors. Specifically, 94% of mothers reported never having eaten fish reported no eating in 1991. Only 30% of women reporting having eaten fish 8+ years between 1955-91 reported no fish consumption in 1991; 70% were still eating fish in 1991. Therefore, we are relatively confident that women who continued to eat fish in recent years (1991 when the cohort was initiated) had been eating over time despite the fish consumption advisories to the contrary. We address this issue on page 7 and in the discussion.
3. We agree that we do not have a formal reliability study of fish consumption. We have edited our discussion of our attempt to assess how well participants in the
New York State Angler Cohort Study reported consumption. Our analysis of these data is limited to frequency of several species of fish. See page 14 for our edits to this end.

Minor Comments
4. We have provided details about model construction and testing including inclusion/exclusion criteria. We apologize for this oversight. See methods, pages 9-10.
5. We prefer to keep the first 10 lines of the “results” section rather than to describe the sample in the methods. Our understanding of methods is to describe what was done and how, and to save results for the results section. (None of the other 3 reviewers asked for this revision. We defer to the editor.)
6. We agree entirely that parental height is an important determinant. However, we did not have these data available. We have edited the sentence to reflect that the explained variance is restricted to study covariates. See page 11.
7. We agree that confidence intervals are more informative than p-values and have included them in lieu of the latter on Table 3.

Reviewer #3 – Longnecker
Major Comments
1. We have clarified fish consumption duration from frequency consistent with Reviewer #2’s comment (see above comment #2). See page 7.
2. The purpose of Table 2 as described in the methods on page 9, is to assess potential effect modification between gestation and birth size. As Table 2 clearly shows, there is no such effect modification. Moreover, the small cell size for preterm infants (<10 events per confounder) would render unstable estimates for the suggested conditional analyses. Table 3 clearly considers other known determinants of birth size in the context of maternal fish consumption. There is no relation between fish consumption and gestation. This distribution is now included on Table 1.
3. As we previously noted, fish consumption had to be forced into the models as it is not a significant predictor of any measure of birth size. Conversely, cigarette smoking is a significant predictor when included with fish consumption or when put into the model alone. We do not show these data given the purpose of this study is to evaluate fish consumption in the context of known determinants.

Minor Comments
[We have elected to not respond to the following suggestions following communication with the editors and the absence of such requests by the 3 other reviewers: 9,11,13,14,15,17,19,21,27,33,34,36,37,38,39,42,45,53,61.]

1. We have retained the word “pregnant women” given that this is the subject matter of the paper. We are not speaking of people in general.
2. We have added chest circumference. See page 2.
3. Yes, the finding is for circumference not circumference percentile.
4. Our exposure is fish consumption not serum PCB concentrations as noted in our paper. We have removed the finding about head circumference from the abstract.
5. We have noted the category of compounds (i.e., polyhalogenated hydrocarbons) considered in previous research including the Yucheng incident. See page 4.
6. Taylor et al. did in fact report the disappearance of an effect after controlling for other factors. Per their abstract, “When gestational age is accounted for in addition to other variables related to birth weight, estimated serum PCB is no longer a significant predictor of birth weight….” Our statement is correct as given. See page 4.

7. While we believe there was sufficient referencing for fish as a dietary source of exposure, we have added a reference specific to fish and diet in the Great Lakes Basin (see reference #16).

8. We believe the point about fish oils and contamination underscores the ubiquitous nature of PCBs underscoring the need to do targeted research on subtle reproductive and developmental outcomes.

9. xx

10. Comprise has been changed to comprised. See page 6.

11. xx

12. As we previously stated on page 7, all participants in the New York State Angler Study were enrolled in 1991. Infants born between 1986-1991 comprise the study sample. See page 7.

13. We wish to state the circumstances surrounding participation. It was voluntary. (page 6)

14. As with comment 13, we wish to state the terms under which we enrolled participants consistent with our IRB approval. (page 6)

15. We prefer to keep the word measures as we cannot evaluate fetal growth that would require a minimum of 3 measurements during gestation. Rather, we have the most extensive set of indicators of fetal growth as measured by birth size. We refer to these indicators as measures of birth size.

16. We disagree about removing the text. All too often investigators overlook the dependent nature of pregnancy outcomes. To this end, we believe it is critical to inform the reader that we have no dependency issues in our analysis. See page 7.

17. xx

18. We have omitted the sentence as suggested.

19. xx

20. See response to Reviewer #2, comment #2.

21. xx

22. We believe the text accurately describes aquatic bioaccumulation as the dietary route of exposure for humans.

23. The word “menstruation” has been changed to “menstrual cycle”. See page 7.

24. To avoid confusion regarding the terms tertiles and quartiles of fish consumption duration depending upon the handling of the “never eaters”, fish duration is operationalized into four categories: none and tertiles of duration. See pages 2 and 8.

25. We have condensed text.

26. The word “inabilities” has been edited to read “…inability of hospital staff…” See page 8.

27. xx

28. The US percentiles are sex specific. See page 8.

29. We use ponderal “indices” to reflect the plural form of index.

30. The extraneous period has been deleted.

31. Since many readers may not be familiar with ponderal indices or head chest ratios, we have kept the sentence. See page 8.
32. Technically, the word operationalized is more precise than recorded. We have left the text as previously written. (page 9)

33. xx

34. xx

35. P<0.05 has been corrected. See page 9.

36. xx

37. xx

38. xx

39. xx

40. The distribution was divided in never eating and tertiles of fish consumption. To clarify, we refer to duration as four categories of years eating. (See pages 2,9.)

41. Model specification along with inclusion/exclusion criteria are cited. See page 10.

42. xx

43. Percentage of mothers covered by health insurance has been added to the text (was originally listed on Table 1). See page 10.

44. The description of the sample from Table 1 data has been edited. See page 10.

45. xx

46. Editorial change made. See page 10.

47. This sentence has been edited in response to the second reviewer’s comment #6. See page 11.

48. We elect to retain the sentence as it clearly states that our exposure is fish consumption and not serum PCBs.

49. We have edited this sentence as a part of revising this paper. See page 12.

50. This text has been previously revised.

51. We state in our purpose and methods that we are interested in known determinants (biologic and other) of fetal growth as measured by birth size. With the exception of cigarette smoking, all covariates are biological determinants that have considerable impact on birth size. We have not restricted our work to biology per se but clearly given the coefficients, we feel justified in arguing for the inclusion of biology when assessing fish consumption and birth size.

52. There is no relation between fish consumption and gestation in this data set as addressed above. Table 2 underscores the absence of effect modification between gestation and birth size.

53. xx

54. We are hesitant to add the word direct, which implies causal analysis has been done.

55. We are unsure of the meaning of this comment.

56. The sentence has been edited.

57. We have previously outlined the major dietary pathways (viz. fish consumption) for exposure to PCBs, especially in the Great Lakes Basin.

58. Our approach for assessing non-response bias in the New York State Angler Cohort Study has been clarified. See page 14.

59. Frequency of consumption is not a nominal (but continuous) variable. See page 14.

60. We hesitate to cite a specific cost for a license, which frequently increases over time and is dependent upon the co-purchase of a hunting license.

61. xx
62. “Long chain n-3” has been inserted before fatty acids. See page 15.
63. We are unable to speak specifically to a recommendation for long chain n-3 fatty acids research.
64. Reference 42 has been edited.
65. The n’s have been subscripted to facilitate reading the table. There is a sizable amount of information but in one table the reader get the complete picture about fish consumption and birth size for preterm, term and postterm infants without having to go further.
66. Table 3 has been edited to include beta coefficients and 95% CIs.

Reviewer #4 – Muckle
Major Comments

The exposure in this study is fish consumption not concentrations of PCBs or methylmercury. We do not have serum concentrations of any compounds for the mothers or infants. We have provided references about sport fish from the Great Lakes and contaminant load for anglers (references 14,16). Methylmercury is typically found in fish such as perch but is not unusually high in sport fish from the Great Lakes as cited in the reference provided. A subgroup of anglers from the overall New York State Angler Study were selected for a validation study and in whom serum concentrations were measured. These data are currently being analyzed but only 15/2,716 mothers in the present study were included. Hence, we are unable to speak to how well self reported consumption correlates or predicts serum concentrations. See pages 7-8.

Minor Comments
1. As addressed above, the sentence is intended to denote the ubiquitous nature of PCBs in fish including fish oil supplements.
2. We address this on page 8.
3. Yes, an obstetrical estimate of gestational age was used. See page 8.
4. The typographical error (missing space) has been corrected.
5. As Table 1 notes, alcohol consumption referred to as the # drinks per month.
6. Table 3 has been revised to include beta coefficients and 95% CIs.
7. Birth defects are a heterogeneous grouping of structural defects. We put it into the model given its potential for impacting birth size. We prefer not to delve into the defects as the real focus of this study is on fish consumption in the context of known determinants of fetal growth and infant birth size. We have noted the heterogeneous grouping on page 9.